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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,843	04/25/2001	Jurgen Bode	BOET 0130 PUS	6703

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/841,843	Applicant(s) Bode et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above, claim(s) *7-9* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 10, and 11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *09/257,561*.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed April 25, 2001, is a continuation of application 09/257,561, filed February 25, 1999, now abandoned, which claims benefit to foreign application 98 103 490.3 filed February 27, 1998 with the EPO.

Election/Restriction

Applicant's election of Group I, claims 1-6, 10 and 11 in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-11 are pending. Claims 7-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 6. Claims 1-6, 10 and 11 are currently under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed with the EPO on February 27, 1998, made under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/257,561, filed on March 25, 1999.

Specification

The abstract of the disclosure is objected to because it contains terms which are not permitted. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided.

Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of a FLP/frt recombinase system in a mouse embryonic cell, comprising the specific steps set forth in claims 1, does not reasonably provide enablement for the practice in other animals. Specifically, the claims require that cells used in the instant method 'can regenerate to complete organisms' (claim 1(c)), however the only cell capable of generating a complete organism is an embryonic stem cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The basis of this rejection focuses on the failure of the instant specification and the art to teach embryonic stem cells for the generation of a transgenic animal other than that for the mouse. The specification teaches a method termed "recombinase-mediated cassette exchange" (RMCE), and relies on the art for the FLp/frt recombination system and the specific culture conditions for use of the method with any potential cell type. In particular, the specification relies on the art for providing embryonic cells which are capable of generating a complete

organism. Currently, only ES cells for the mouse are available (reviewed in Seamark and Moreadith *et al.*). Since the specification relies on the art for the appropriate cells which are capable of generating a complete organism, it is subject to the same limitations recognized in the art. In the instant case, the only cells described in the art capable of generating a complete organism are mouse embryonic stem cells. The specification provides no specific guidance on isolating or culturing totipotent embryonic stem cells from any vertebrate species. Neither the instant specification, nor the art of record, has resolved the many complexities involved in isolating embryonic stem cells from other species besides the mouse.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is unclear in the recitation of 'repetitive' in the preamble because it is not clear if the exchange of the cassette will happen multiple times during the method steps or that the

cassette is capable of being replaced multiple times. It is noted that the specification teaches '"recombinase-mediated cassette exchange" (RMCE)', however the general term used fails to clearly set forth the intended use of RMCE. Additionally, claim 1 is unclear in the recitation of 'for tagging' in step (a) because it is not clear what is being tagged, the FRT site, a specific side of the marker construct, or the whole cassette. 'Tagging' as used in the art has a broad use and meaning, and should be defined in the claim or the specification to clearly describe Applicants use of the term. The context of the term is ambiguous and does not clearly reflect any specific intent. Dependent claims are included in the basis of the rejection because they fail to further clarify the basis of the specific rejections.

Claim 10 is incomplete in that it is a method claim for the generation of transgenic vertebrates, however it does not recite method steps on how to obtain said animal.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Shlake *et al.* (Biochemistry, 1994).

Schlake *et al.* teach a method of modifying the genome of a cell by; first inserting a positive/negative selection cassette flanked by heterologous FRT sites including F_3 spacer mutants into a cell, second, initiating exchange of the positive/negative cassette with a plasmid containing a second cassette comprising a gene flanked by two heterologous FRT sites which are complementary to those of the positive/negative cassette (page 12748; figure 2). More specifically, Schlake *et al.* teach a method of RMCE as set forth in the instant specification. First, Schlake *et al.* teach a stable integration of $HygTkF_n$ (pOG44) into CV-1 and BHK cells which is achieved by positive selection (page 12747; column 2). Further, Schlake *et al.* teach the various FRT spacer sites and the most preferred combinations for use of these (Table 1 and discussion section). Finally, motivated by success of mixed vector example, Schlake *et al.* teach that one can perform the reaction with a stable chromosomal copy of $HygTkF_n$ (page 12750; bridging paragraph of column 1 and 2). Further, Schlake *et al.* teach one can use the technique in other cell types including mouse ES cell lines.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* in view of Jung *et al.*

Shlake *et al.* teach a method of modifying the genome of a cell by; first inserting a positive/negative selection cassette flanked by heterologous FRT sites including F_3 spacer mutants into a cell, second, initiating exchange of the positive/negative cassette with a plasmid containing a second cassette comprising a gene flanked by two heterologous FRT sites which are complementary to those of the positive/negative cassette (page 12748; figure 2). More specifically, Schlake *et al.* teach a method of RMCE as set forth in the instant specification. First, Schlake *et al.* teach a stable integration of $HygTkF_n$ (pOG44) into CV-1 and BHK cells which is achieved by positive selection (page 12747; column 2). Further, Schlake *et al.* teach the various FRT spacer sites and the most preferred combinations for use of these (Table 1 and discussion section). Finally, motivated by success of mixed vector example, Schlake *et al.* teach that one can perform the reaction with a stable chromosomal copy of $HygTkF_n$ (page 12750; bridging paragraph of column 1 and 2). However, while there is mention of mouse ES cell lines, they do not teach to use said method to create cells which are capable of generating an animal.

Jung *et al.* teach a method using an ES cell modified by FLP recombinase to generate a transgenic animal (page 986; figure 4). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods of Shlake *et al.* modify the genome of an ES cell using FLP recombinase to create a transgenic animal as described by Jung *et al.* One having ordinary skill in the art would have been motivated to use the method of Shlake *et al.* to obtain transgenic animals without extraneous genes that may influence the transgene behavior as described by Jung *et al.* (page 984-5; bridging paragraph). There would have been a reasonable expectation of success given the results of Jung *et al.* to create a transgenic animal by the method described in Schlake *et al.* to modify ES cells.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlake *et al.* in view of Ludwig *et al.*

Shlake *et al.* teach a method of modifying the genome of a cell by; first inserting a positive/negative selection cassette flanked by heterologous FRT sites including F_3 spacer mutants into a cell, second, initiating exchange of the positive/negative cassette with a plasmid containing a second cassette comprising a gene flanked by two heterologous FRT sites which are complementary to those of the positive/negative cassette (page 12748; figure 2), but do not teach to use a cell which is capable of generating an animal. Ludwig *et al.* teach a method to modify

the genome of a fertilized one cell egg using FLP recombinase (page 389; figure 2). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods of Shlake *et al.* modify the genome of fertilized egg using FLP recombinase to create a transgenic animal as described by Ludwig *et al.* One having ordinary skill in the art would have been motivated to use the method of Shlake *et al.* to mediate plasmid-to-chromosome targeting of a gene as described by Ludwig *et al.* (page 385; last line of abstract). There would have been a reasonable expectation of success given the results of Ludwig *et al.* to create a transgenic animal by the method described in Schlake *et al.* to modify a fertilized egg in order to generate a transgenic animal.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Prior art made of record deemed pertinent to the instant invention:

Wahl *et al.* (US Patent 5,654,182) describes the use of FLP/frt recombination system to alter the genome of a cell and proposes using the system to make targeted alterations in complete organisms, however Wahl *et al.* does not teach frt mutants.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

RAM R. SHUKLA, PH.D
PATENT EXAMINER